inducing activity of TGF-β in contact with the cell, and wherein the agent is not a general protein synthesis inhibitor.--

--28. (New) The method of claim 27 wherein the cell is a mesangial cell.--

--29. (New) The method of claim 27 wherein the proteoglycan is selected from the group consisting of biglycan and decorin.--

REMARKS

Claims 1-20 are pending in this application. Claims 1, 2, 5-7, 10, 13-15, 19 and 20 are under consideration, the other claims being withdrawn as directed to a non-elected invention. Applicants have canceled claims 1, 2, 5-7, 10, 13-15, 19 and 20 without prejudice. Applicants have added new claims 21-29, which they request to be entered for examination.

The amended claims do not add new matter. The language of claim 21 that refers to agents that "bind to TGF-ß" finds support in the specification on page 9, line 36 to page 10, line 1.

I. REJECTIONS UNDER DOUBLE PATENTING DOCTRINE

The claims stand provisionally rejected for obviousness-type double patenting over claims in co-pending applications 07/467,888 and 07/803,285. Applicants acknowledge the provisional rejection and wish to defer the issue until an indication of allowance.

II. REJECTIONS UNDER 35 U.S.C. § 112

A. Enablement And Definiteness Of Claimed "Agents"

Claims 1, 2, 5-7, 10, 19 and 20 stand rejected under 35 U.S.C. § 112, first and second paragraphs on the ground that the specification is not commensurate with the scope of the claimed agents and further that the claims are vague in the scope of the term "agents." Applicants request reconsideration.

The Office Action stated that although the term "agent" was defined by its ability to suppress accumulation of extracellular matrix, it was not defined in terms of its ability to bind TGF-β and, therefore, that the claims read on general protein synthesis inhibitors. Applicants have canceled claim 1 in favor of claim 21. Claim 21 is directed to agents which have the characteristics of binding to TGF-β and suppressing the accumulation of a TGF-β-induced component of the extracellular matrix. This amendment satisfies the Examiner's concerns regarding scope and definiteness of the term "agents."

The Examiner further stated that the specification shows only evidence of suppression of accumulation of biglycan and decorin. Applicants traverse this ground of rejection. First, experiments using periodic acid-Schiff (PAS) staining clearly show that the inhibition of TGF-β suppressed production of the entire extracellular matrix (ECM). (Example II, pages 17-18, Figure 7 and Figure 8.) As the art was aware, PAS stains glycoproteins in tissues, including collagens (interstitial and basement membrane), fibronectin and laminin, thus allowing one to visualize the ECM. (See, for example, Chapters 9 and 10 in

Theory and Practice of Histology, D.C. Sheehan and B.B. Hrapchak, 2nd Edition, 1980 (Battelle Press, Columbus, Ohio)). These molecules are all components of the ECM. Bruijn et al., J. Lab. Clin. Med., 111:140-149 (1988). Electron microscopy, which permits visualization of bundles of collagen fibrils as well as the ultrastructure of the entire ECM, confirms the effect on the entire ECM. Okuda et al., J. Clin. Invest., 86:453 (1990). Therefore, the data do not indicate that accumulation of decorin and biglycan were exclusively suppressed.

Second, Applicants focused on suppression of decorin and biglycan as markers of TGF-β activity, not of ECM. TGF-β induces the production of many macromolecules in the ECM. However, Applicants demonstrated that among several cytokines (PDGF, IL-1, TNF and TGF-β), decorin and biglycan are specifically induced by TGF-β. Therefore, if an agent inhibited the production of decorin and biglycan, this would indicate that the agent inhibited the activity of TGF-β. The fact that inhibiting TGF-β suppressed production of decorin and biglycan does not mean that other components were not also suppressed.

Thus, examination of decorin and biglycan production showed that anti-TGF-β inhibited the activity of TGF-β and not something else; and PAS staining demonstrated that inhibition of TGF-β by anti-TGF-β suppressed accumulation of the entire ECM. Therefore, Applicants are entitled to claim suppression of accumulation of ECM by inhibition of TGF-β.

Furthermore, in claims 21-26 Applicants are claiming a method of treating a pathology. Applicants need not understand the mechanism of their invention. The Examiner's requirement to

include a mechanism in the claim amounts to a penalty on Applicants for having elucidated and disclosed elements of the activity of TGF-β at the molecular level. Such a penalty frustrates the purpose of the patent laws to promote the progress of science and the useful arts.

B. Enablement Of Claimed Pathologies

Claim 5 stands rejected under 35 U.S.C. § 112, first paragraph on the ground that the specification enables claims only to treatment of glomerulonephritis. The Office Action stated that "the effects of TGF-beta are not well enough defined to provide a method of treating other diseases such as cirrhosis and ARDS." In support of this statement the Office Action cited Gressner for the proposition that the pathobiology of cirrhosis changes over time and, therefore, the use of anti-TGF-β is not established. Applicants traverse.

It is not necessary for utility that the claimed method be effective at every stage of pathology. The specification demonstrates effectiveness of the invention. Effectiveness at any stage suffices for utility.

Referring to the articles cited by Applicants in a previous response, the Examiner stated further that the specification was not enabling at the time the invention was made. In fact, the specification objectively enables the invention. It shows how to treat pathologies characterized by the TGF-β-induced production of extracellular matrix in a tissue: by contacting the tissue with an agent that suppresses the activity of TGF-β. Applicants are not relying on the cited

documents to enable the invention, but merely to confirm that the invention will work in cirrhosis and ARDS, just as the specification indicates. Evidence in these articles establishes beyond mere speculation that TGF-ß does induce extracellular matrix production in cirrhosis and ARDS. Therefore, Applicants are entitled to claim the use of the invention in these diseases.

Accordingly, Applicants request withdrawal of the rejections for lack of enablement and indefiniteness.

Finally, Applicants have added claims 22 and 25. Both specify treating glomerulonephritis. Therefore, these claims are directed to a disease that the Examiner has already agreed is enabled.

C. Enablement Of Agents Beyond Antibodies

Claims 1, 6, 10, 19 and 20 stand rejected under 35 U.S.C. § 112, first paragraph on the ground that the disclosure allegedly is enabling only for claims limited to the use of antibodies. The Examiner maintained her rejection that it was not apparent that certain agents would have the same effect as antibodies since those agents "are not specific for TGF-beta." Applicants traverse.

Insofar as they encompass Arg-Gly-Asp peptides, the Examiner objects to the claims on the ground that "results obtained using an in vitro assay system do not necessarily extrapolate to an in vivo effect." Applicants do not agree that in vitro results with Arg-Gly-Asp peptides cannot be extrapolated to in vivo situations and they reserve the right to pursue claims

to the use of these peptides in other applications. However, in order to expedite prosecution, Applicants have canceled the pending claims in favor of added claims 21-29, which are directed to agents that bind TGF-β.

Finally, in their last response, Applicants cited Border et al. to demonstrate that another agent that binds to TGF-β, decorin, also works in the method of the invention. The Examiner was concerned that the specification did not provide support for the information contained in this reference. However, as above, Border et al. was not cited to enable the invention, but to corroborate the teachings in the specification that the invention has utility in the use of agents other than antibodies that bind to TGF-β and suppress the accumulation of ECM. Decorin falls within the class of agents that bind to TGF-β and suppress the accumulation of ECM.

D. Definiteness of "General Protein Inhibitor"

The Examiner rejected claim 13 under 35 U.S.C. § 112, second paragraph as indefinite in the use of the term "general protein inhibitor." The Examiner suggested the term "protein synthesis inhibitor." Applicants have canceled claims 13-15 in favor of claims 27-29, which incorporate the term "general protein synthesis inhibitor."

Upon removal of this indefiniteness rejection, claims 13-15 (now 27-29) will stand only provisionally rejected for double patenting. Accordingly, Applicants request the Examiner withdraw the provisional double patenting rejection pursuant to MPEP § 804 and allow claims 27-29.

III. REJECTIONS UNDER 35 U.S.C. § 103

The claims stand rejected under 35 U.S.C. § 103 as obvious over Conner et al. or over Conner et al. in light of MacKay et al. Conner et al. fails on its own terms, as Applicants will demonstrate below. However, this failure is even more apparent when the article is placed in the context of the understanding in the art at Applicants' filing date of the physiological role of TGF-β and its use as a therapeutic agent.

A. At The Time Of Filing TGF-β Was Primarily Understood As A Promoter Of Tissue Repair

At the time of the invention, the physiological function of TGF-β was only partially understood. Evidence showed that TGF-β stimulated angiogenesis and fibrosis, two activities considered normal and advantageous parts of wound healing. Roberts et al., Proc. Natl. Acad. Sci., USA, 83:4167-71 (1986).

Evidence such as this gave researchers hope that TGF-β would find use as a therapeutic agent to accelerate healing. Indeed, the late 1980's and early 1990's saw experiments in which TGF-β was applied to wounds to enhance healing by promoting ECM production. See, e.g., Mustoe et al., Science, 237:1333-36 (1987), Quaglino, Jr. et al., Lab. Invest., 63:307-319 (1990) and Quaglino, Jr. et al., J. Invest. Derm., 97:34-42 (1991). Mustoe et al. stated in the abstract that "TGF-β is thus a potent pharmacological agent that can accelerate wound healing in rats." Thus, the literature shows a general consensus that wound healing could be promoted by administration of TGF-β.

B. The Effect of Suppressing TGF-ß Activity In Pathogenic Fibrosis Could Not Have Been Predicted At The Time

While the art showed that administration of TGF-ß accelerated wound repair, the role of TGF-ß in pathological fibrosis was not understood. The physiological response in repair is very complex. The effect of inhibiting TGF-ß activity in this response was unpredictable at the time. On one hand, it might have no effect due to redundant action of other cytokines. On the other hand, it might so upset the biological response as to prevent wound healing altogether. To Applicants' knowledge, no art at the time provided a reasonable expectation that blocking TGF-ß activity, alone, would be a successful method of treating pathologic fibrosis.

C. Applicants Demonstrated That Suppressing TGF-ß Activity Inhibits Fibrosis Without Interfering In The Repair Process

Applicants' important contribution to the art was the discovery that inhibiting TGF-ß activity sufficed to suppress pathologic fibrosis without adversely interfering in the repair process. This contribution was recognized in Sporn and Roberts, J. Clin. Invest., 92:2565-66 (1993), page 2565, second column. At a presentation given by Applicant Wayne Border, at the CIBA Foundation Symposium, Dr. Sporn referred to the work as "an exciting first approach to a nasty clinical problem." 1991 Clinical Applications of TGF-ß, Wiley, Chichester (Ciba Foundation Symposium 157), pages 178-193 (quote on page 189).

D. Conner Et Al. Provides Neither The Suggestion To Suppress TGF-β Activity To Prevent Pathological Fibrosis Nor The Reasonable Expectation That Such Action Would Succeed

Read in light of the general understanding of the time, Conner et al. does not render the invention obvious. Conner et al. begins with the recognition of the time that TGF-β appears to have a role in the fibrotic process and cites the experiments of Roberts et al., supra, showing that TGF-β induced angiogenesis and fibrosis. Conner et al., page 1661, second column. The authors then ask if TGF-β can be correlated with the degree of fibrosis. To find out, they quantified the amount of TGF-β in intraocular fluid of fibrotic eyes using the mink lung assay. Conner et al., page 1662, "Quantification of TGF-β."

The mink lung assay is a quantitative test for TGF-β. TGF-β inhibits the growth of mink lung cells. In the assay, mink lung cells were exposed to a sample of intraocular fluid alone to determine if growth was inhibited, and then to the same sample of intraocular fluid with anti-TGF-β antibodies to determine if growth was restored. In this way, the presence of TGF-β was detected and its quantity measured.

Conner et al. report a correlation between the quantity of TGF-β and the degree of fibrosis. What did this correlation mean? In the authors' words, "[t]he final determination of the role of TGF-β in this disease process awaits the ability to block its activity and assess if this can retard or arrest fibrosis." Conner et al., sentence bridging pages 1665-1666.

A person of ordinary skill in the art reading this statement in the context of the article and the understanding of the time would likely conclude that the authors (1) were not sure what the role of TGF-β in fibrosis was and (2) did not know of any agents that block TGF-β activity in this system.

The first conclusion is further supported by the authors' experiment in which TGF-β was administered to the eye in an attempt to induce fibrosis. Less than half the treated animals demonstrated fibrosis in response to TGF-β, suggesting against a cause and effect relationship. (Conner et al., page 1664, last paragraph.)

Therefore, this statement is not a recognition that fibrosis can be treated by inhibiting TGF-β activity. It is little more than an invitation to determine the role of TGF-β in ocular fibrosis. The article provides neither the reasonable expectation that intraocular fibrosis could be treated by inhibiting TGF-β activity nor the means to do so. Applicants' specification provides a solution to both of these problems.

In fact, as opposed to inhibiting TGF-β activity in intraocular tissue, researchers have successfully applied TGF-β to heal localized lesions in the human eye. Sporn and Roberts, supra, last paragraph of page 2565.

E. The Office Action Contains Factual Inaccuracies

In regard to the disclosure of Conner et al., a certain statement in the Office Action requires reconsideration. The Office Action stated that "[s]ince anti-TGF-beta was shown to

block activity of TGF-beta and TGF-beta was shown to increase intraocular fibrosis, . . . , one of the activities which was inhibited by anti-TGF-β was the blocking of [sic] ECM production." This statement is factually inaccurate. Conner et al. did not show that anti-TGF-β blocked ECM production in intraocular tissue or, for that matter, any other tissue. They did not introduce anti-TGF-β into intraocular tissue. Conner et al. used anti-TGF-β in the mink lung assay to quantify the amount of TGF-β in intraocular fluid. This assay measures inhibition of cell growth, not promotion of ECM production. The article provides no evidence of an activity of TGF-β in intraocular fibrosis.

F. MacKay Et Al. Does Not Cure The Deficiencies of Conner Et Al.

Regarding the rejection of claims over Conner et al. in light of MacKay et al., Applicants explained the deficiencies of MacKay et al. in their prior amendment and continue to stand by that position. Furthermore, Applicants have explained in the preceding discussion why Conner et al. does not make the invention obvious. MacKay et al. does not suffice to fill the gap.

CONCLUSION

In light of the foregoing amendments and remarks, Applicants respectfully request the Examiner to withdraw all rejections and to allow the claims under consideration. Applicants invite the Examiner to call Cathryn Campbell, Esq., or the undersigned attorney if there are any remaining issues.

Respectfully submitted,

Date: February 11, 1994

John R. Storella
Registration No. 32,944
Telephone: (619) 535-9001
Facsimile: (619) 535-8949

CAMPBELL AND FLORES
4370 La Jolla Village Drive
Suite 700
San Diego, California 92122